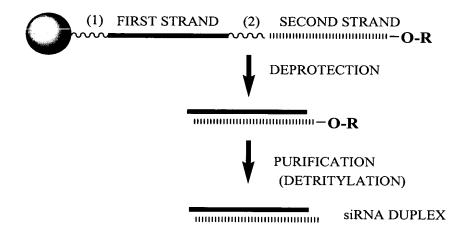
Figure 1



= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

= CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
(2) INVERTED DEOXYABASIC SUCCINATE)

= CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

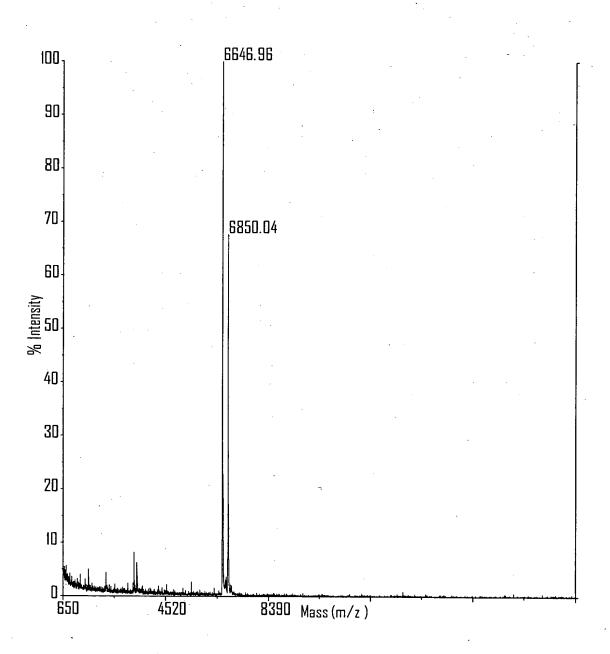
Inventor: McSwiggen et al.

Title: RNA Interference Mediated Inhibition of Vascular Edothelial Growth Factor And Vascular Edothelial Growth Factor Receptor Gene

Attorney Docket No. MBHB02-742-F (400/131)

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Figure 2



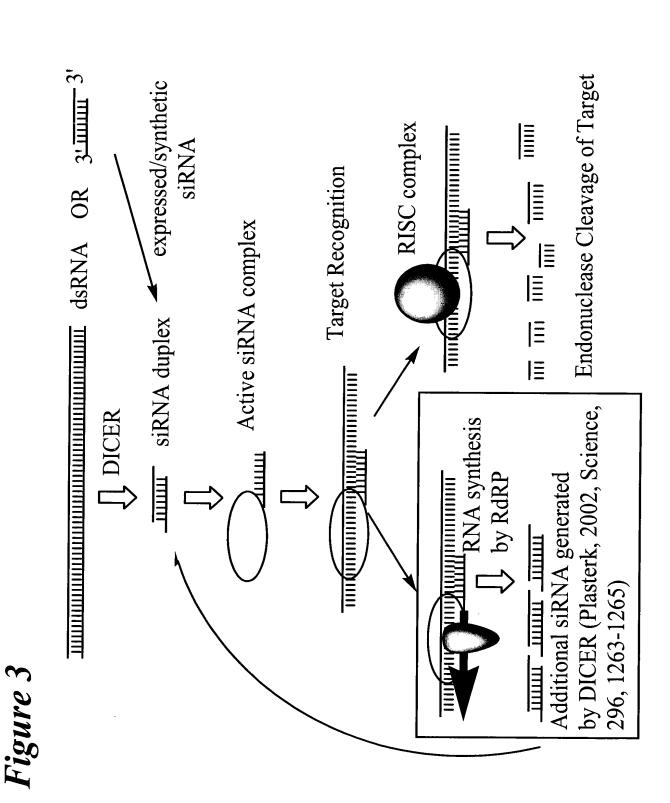


Figure 4

	SENSE STRAND (SEQ ID NO 2438) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
A		3'
A	3	5'
	ANTISENSE STRAND (SEQ ID NO 2439) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 2440) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N)	
_	5'- NNNNNNNNNNNNNNNNNNNNNNNN -3	3'
B	3'- L-(N _s N) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	5' }
	ANTISENSE STRAND (SEQ ID NO 2441) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N 1)	4)
		Ś
	SENSE STRAND (SEQ ID NO 2442) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)	
C	$\int 5'$ - B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	3' [
	$3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNN -	5'
	ANTISENSE STRAND (SEQ ID NO 2443) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	
	SENSE STRAND (SEQ ID NO 2444) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOX	
_	5'- B-N N N N N N N N N N N N N N N N N N	
D	$3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	7
	ANTISENSE STRAND (SEQ ID NO 2441) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N	
	SENSE STRAND (SEQ ID NO 2445) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	ĺ
	5'- B-NNNNNNNNNNNNNNNNNNNNNN-B -3'	
\mathbf{E}	3'- L-(N _s N) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	l
	ANTISENSE STRAND (SEQ ID NO 2441) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N)
		ر ۲
	SENSE STRAND (SEQ ID NO 2444) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	7
F	5'- B-NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	
r;	$3'$ - L- (N_sN) NNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	۲ '
	ANTISENSE STRAND (SEQ ID NO 2446) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY	,
	-	1

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

- B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT
- L = GLYCERYL MOIETY THAT IS OPTIONALLY PRESENT
- S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE

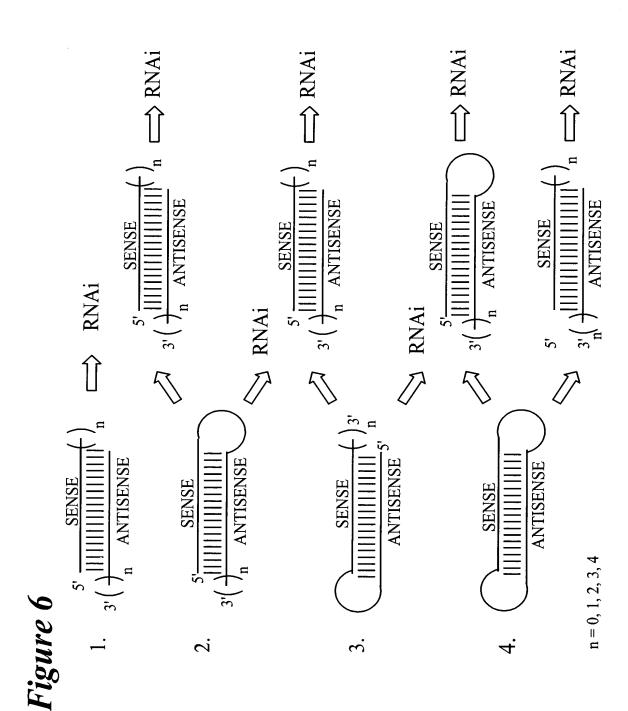
Figure 5

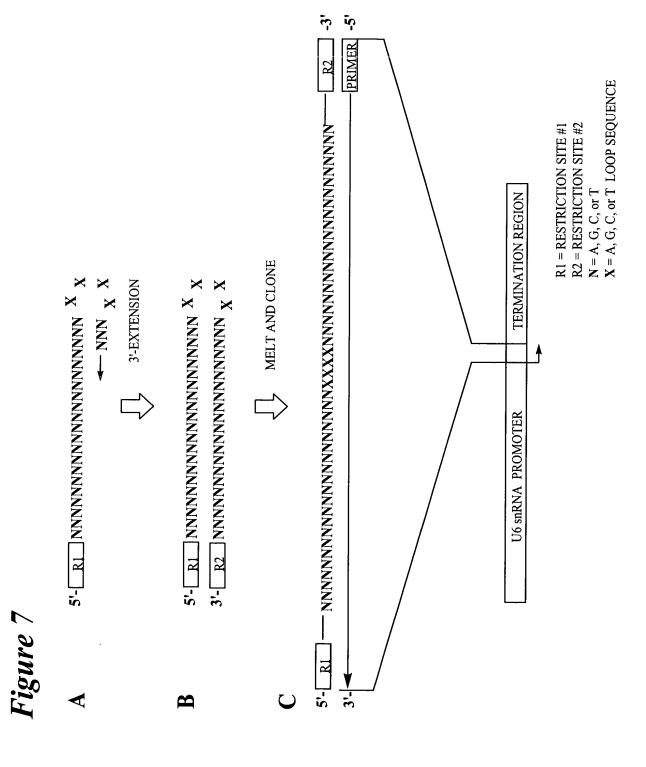
	_		
		SENSE STRAND (SEQ ID NO 2447)	
•	5'-	iB-UCUGAUGAUGUCAGAUAUG <i>TT</i> -iB	-3'
A	₹ 3'- •	L-T _S TAGACUACUACAGUCUAUAC	-5'
		ANTISENSE STRAND (SEQ ID NO 2448)	
		711 (115 E 15 E 5 11 E 115 (5 E Q 16 17 E 2440)	
		SENSE STRAND (SEQ ID NO 2449)	j
_	5'-	u c u g <u>a</u> u g <u>a</u> u g u c <u>a g a</u> u <u>a</u> u g T _S T	-3'
B	₹ 3'-	L-T _S T <u>a g a c u a c u a c a g u c u a u a c</u>	-5' }
		ANTISENSE STRAND (SEQ ID NO 2450)	
		SENSE STRAND (SEQ ID NO 2451)) }
		SENSE STRAND (SEQ ID NO 2431)	
	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
C	4 3'-	L-T _S T A G A c u A c u A c A G u c u A u A c	-5' >
		ANTISENSE STRAND (SEQ ID NO 2452)	
	Č		7
		SENSE STRAND (SEQ ID NO 2453)	
D	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
D	3'-	L-T _S T <u>a g a c u a c u a c a g u c u a u a c</u>	-5'
		ANTISENSE STRAND (SEQ ID NO 2450)	
			J
		SENSE STRAND (SEQ ID NO 2454)	ĺ
	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
${f E}$	₹ 3'-	L-T _S Tagacuacuacagucuauac	-5'
		ANTISENSE STRAND (SEQ ID NO 2450)	
		(624 12 110 2120)	
			Ţ
		SENSE STRAND (SEQ ID NO 2453)	
	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
F	₹ 3'-	L-T _S TAGAcuAcuAcAGucuAuAc	-5'
		ANTISENSE STRAND (SEQ ID NO 2455)	_
		(52(121.62)	ŀ
			ノ

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro italic lower case = 2'-deoxy-2'-fluoro underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY
B = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY OPTIONALLY PRESENT

S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE





Inventor: McSwiggen et al.

Title: RNA Interference Mediated Inhibition of Vascular Edothelial Growth Factor And Vascular Edothelial Growth Factor Receptor Gene

Attorney Docket No. MBHB02-742-F (400/131)

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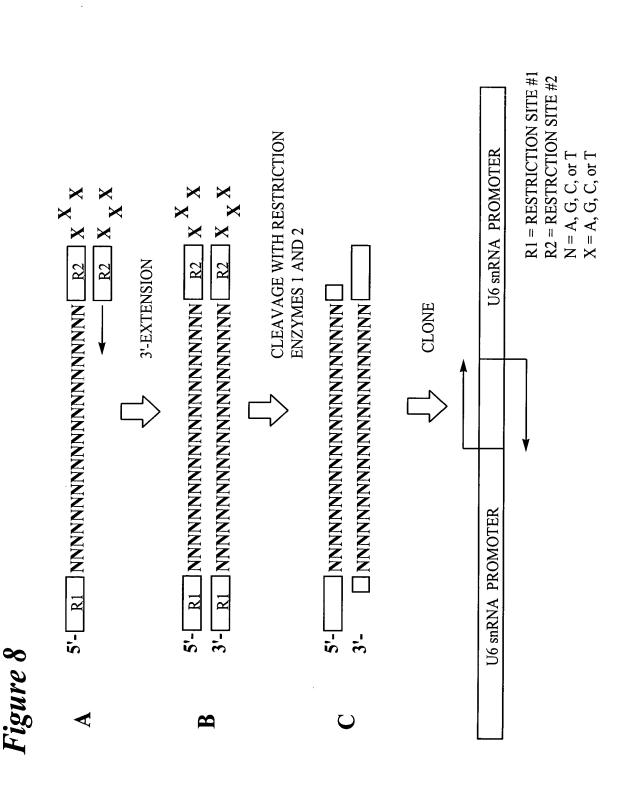
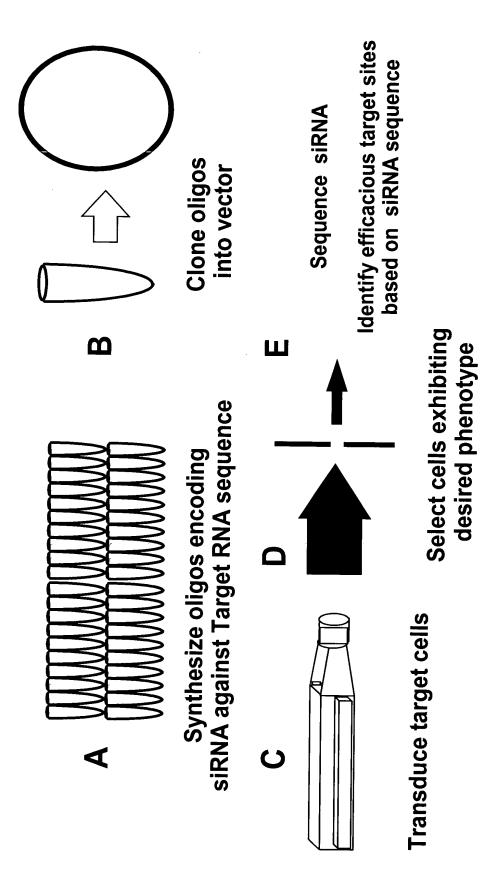
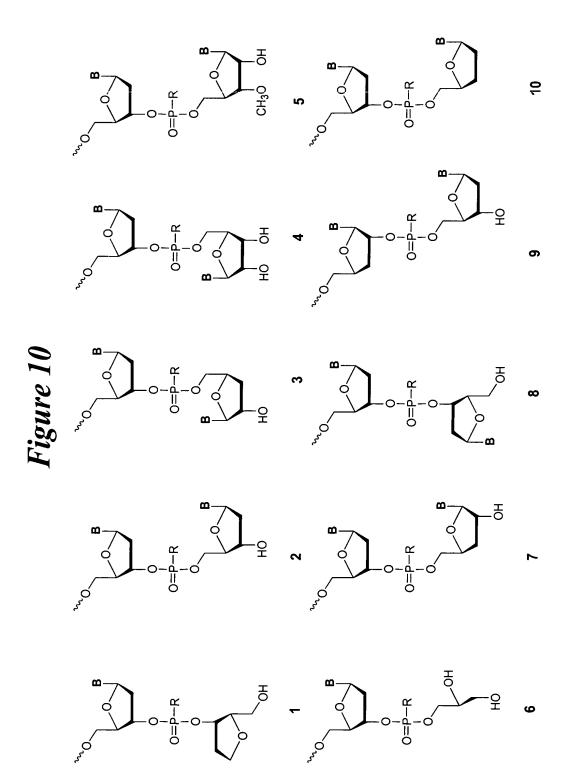


Figure 9: Target site Selection using siRNA





R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy

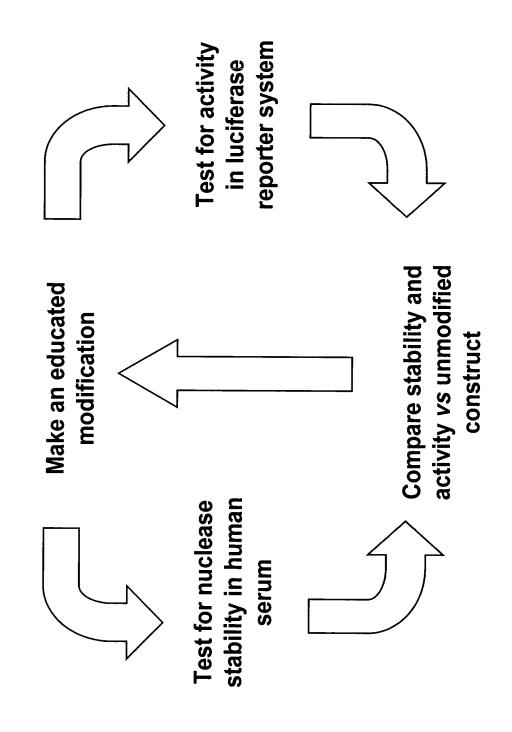


Figure 12: Inhibition of VEGF-Induced Angiogenesis **VEGF Control** Inactive 1ug RPI 29983/29984 Inactive 3ug RPI 29983/29984 *p< 0.05 with respect to VEGF by Dunnett's **p<0.05 with respect to Inverted control by Tukey-Kramer Inactive 10ug RPI 29983/29984 Active 1ug 8년 79696758699 Active 3ug 86967/56967 I심심 Active 10ug 요한 29695/29699 20 80 9 40 0 Angiogenesis % Inhibition of VEGF induced

Figure 13: A375 24h 36B4 VEGFR1 mRNA Expression

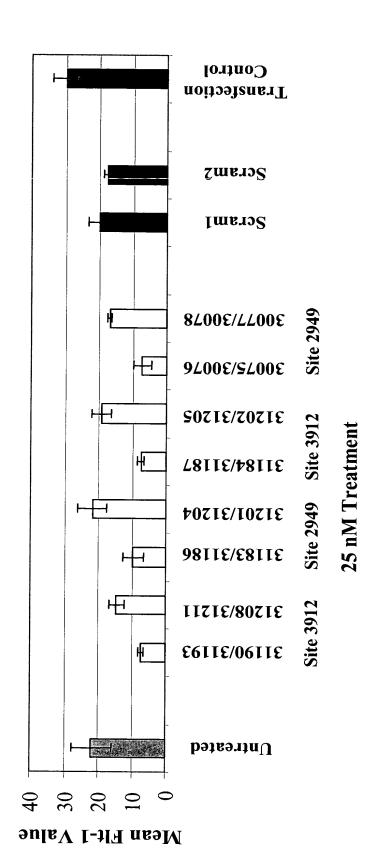
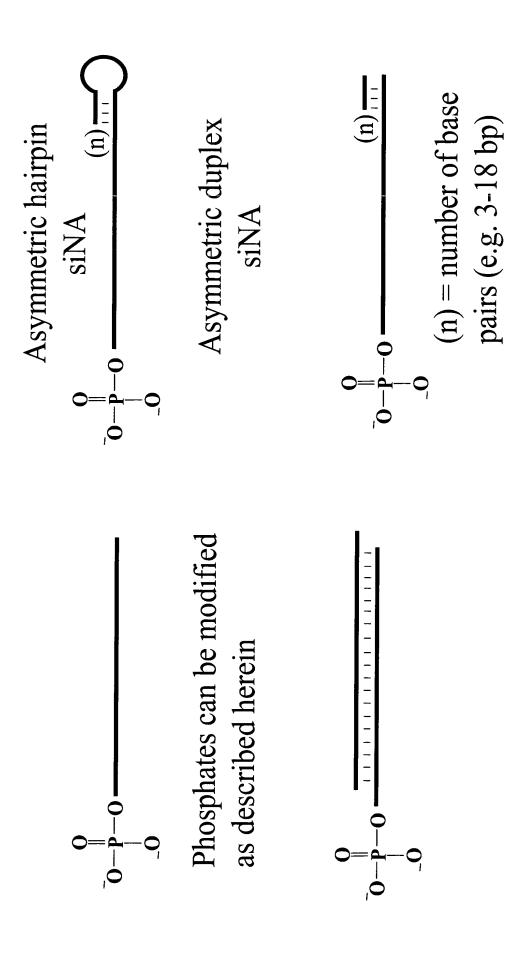


Figure 14: Phosphorylated siNA constructs



modifications herein

Figure 15: 5'-phosphate modifications

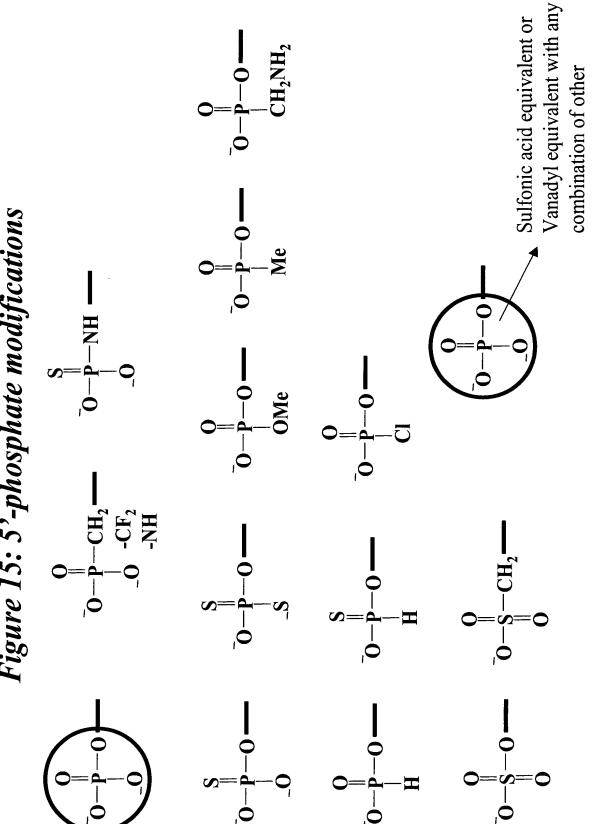
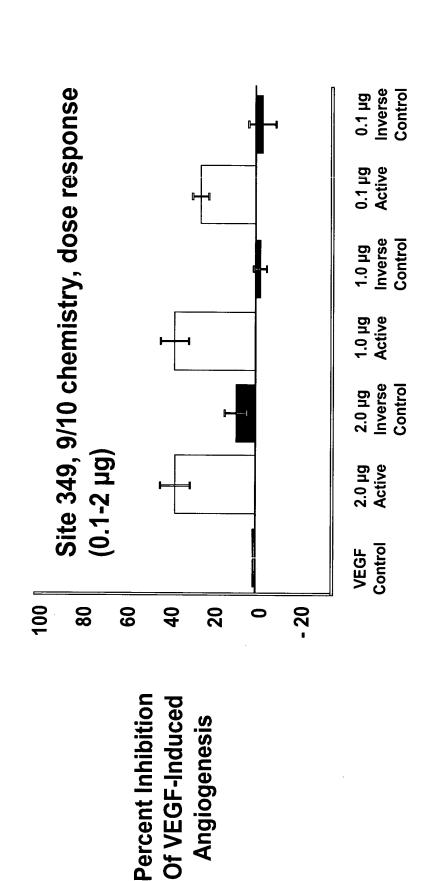
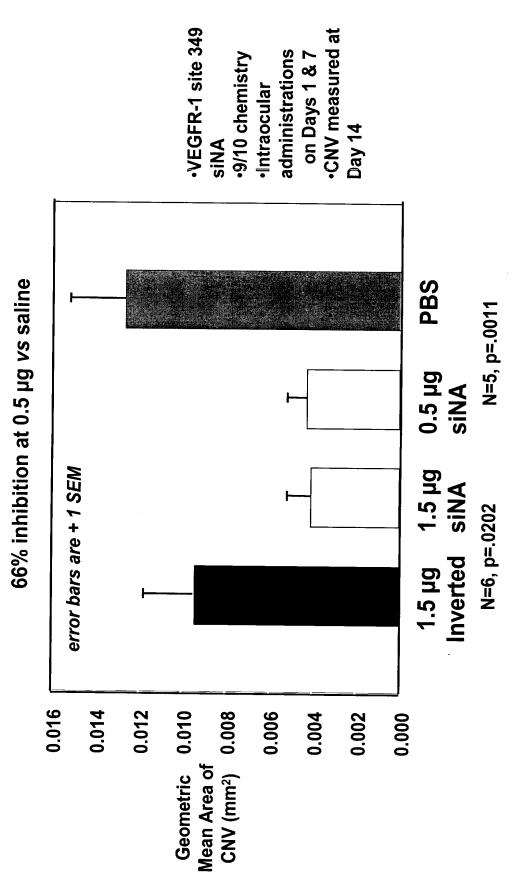


Figure 16: siNA Targeting VEGFR-1 Inhibits VEGF-Induced Rat Corneal Angiogenesis

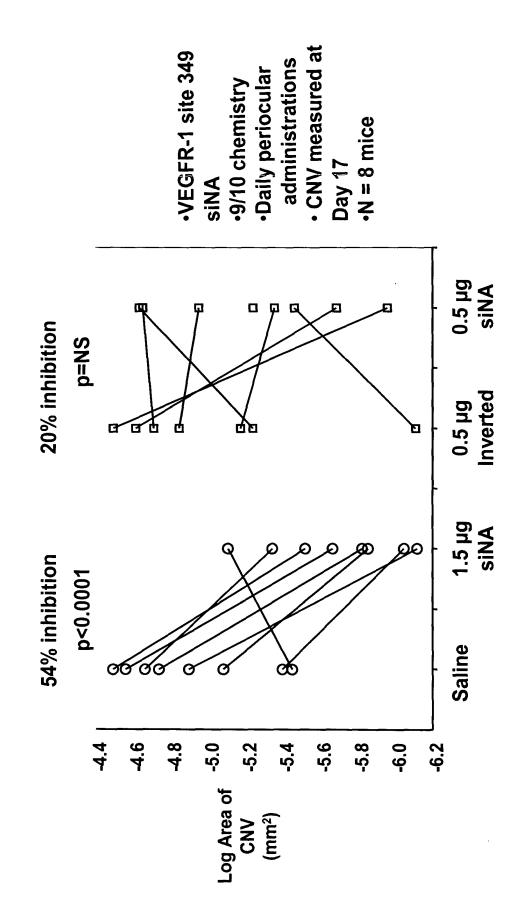


anti-VEGFR-1 siNA (intraocular administration) Figure 17: Inhibition of Mouse CNV with

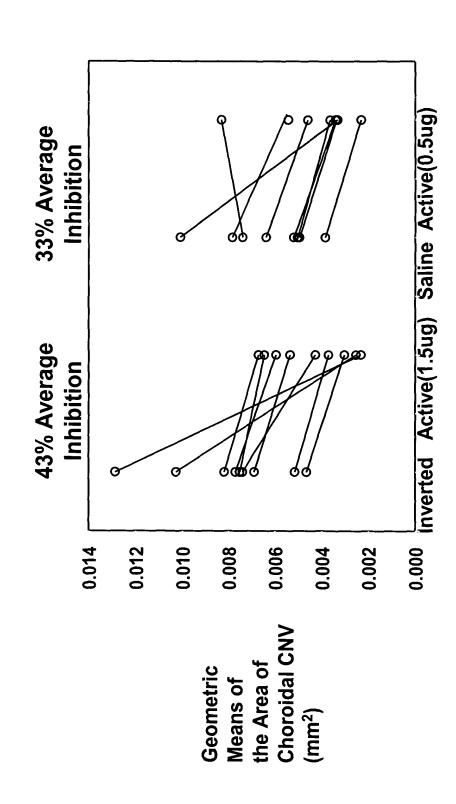
57% inhibition at 1.5 µg vs inverted control



anti-VEGFR-1 siNA (periocular administration) Figure 18: Inhibition of Mouse CNV with



anti-VEGFR-1 siNA (periocular administration) Figure 19: Inhibition of Mouse CNV with



N=8 mice, p=.0187

N=9 mice, p=.0034